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Canadian Adverse Drug Reaction Newsletter

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Adverse drug reaction reporting - 2000: Part 1

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 7361 domestic reports of suspected adverse drug reactions (ADRs) in 2000. The ADRs were reported for the most part by health professionals (pharmacists, physicians, nurses, dentists, coroners and others), either directly to the CADRMP or indirectly through another source (Table 1). A further analysis of the total number of reports by reporter type (originator) is outlined in Table 2.

Of the ADR reports received, 3343 were classified as serious. A serious ADR is defined in the Food and Drugs Act and Regulations as "a noxious and unintended response to a drug which occurs at any dose and requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death." Several suspected reactions may be listed in one ADR report. A total of 18 349 suspected serious and non-serious reactions were included in the 7361 domestic reports.

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Table 1: Source of reports of adverse drug reactions (ADRs) received by the CADRMP in 1999 and 2000

Source	No. (and %) of reports received			
	1999		2000	
Manufacturer	2750	(48.3)	3630	(49.3)
Regional ADR centre	2506	(44.1)	2595	(35.3)
Other*	432	(7.6)	1136	(15.4)
Total	5688	(100.0)	7361	(100.0)

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program.
*Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients.

Table 2: Number of ADR reports by type of reporter (originator) in 1999 and 2000

Reporter	No. (and %) of reports received			
	1999		2000	
Pharmacist	2103	(37.0)	2420	(32.9)
Physician	1446	(25.4)	1876	(25.5)
Health professional*	1051	(18.5)	1157	(15.7)
Consumer/patient	516	(9.1)	1010	(13.7)
Nurse	447	(7.9)	381	(5.2)
Other	125	(2.2)	517	(7.0)
Total	5688	(100.0)	7361	(100.0)

*Type not specified in report

The CADRMP would like to thank all who have reported ADRs for their contribution to the program. Additional discussions (Part 2) will follow in the July 2001 issue of the Newsletter.

Written by: Heather Sutcliffe, BScPharm, Bureau of Licensed Product Assessment.

Antiparkinsonian drugs and "sleep attacks"

Ropinirole (Requip) and pramipexole (Mirapex) are 2 non-ergoline dopamine agonists approved for use in Canada in August 1997 and January 1998, respectively, both as monotherapy in early Parkinson's disease and as adjunct therapy in advanced Parkinson's disease.[1,2]

In 1999 a report was published describing 8 cases of sudden onset of sleep, all originating from the same clinical centre in the United States and associated with pramipexole treatment.[3] In one case the patient was switched from pramipexole to ropinirole therapy. A hypothesis was formulated by the authors that these drugs may have played a causative role in dysregulating dopaminergic input to the brain's reticular activating system, which controls sleep and arousal.[3] Since then, there have been numerous replies to this article, highlighting this public health issue and the difficulties inherent in defining the target population at risk of sudden onset of sleep.[4,5]

The true nature of this adverse reaction remains to be established; reliable epidemiological and polysomnographic studies have yet to be published. Some authors have suggested that this is a drug class effect inherent to all dopamine agonist antiparkinsonian medications.[6] Furthermore, disturbances in sleep pattern and wakefulness have been previously established for Parkinson's disease irrespective of medication use.[6] Reasons for sleep disturbance in this population may include age-related deterioration in sleep architecture, sleep fragmentation, motor disturbances of Parkinson's disease (e.g., dyskinesia), use of alcohol and other underlying sleep disorders. All of these can potentially result in increased daytime sleepiness with enhanced sensitivity to sedating medications.[6]

The issue of ropinirole and sleep disorder was referred to in the Communiqué section of this Newsletter in October 1999 to promote awareness in the health care community and to encourage reporting of this potential ADR.[7] Although initial reports of adverse reactions submitted to the CADRMP related to ropinirole had been varied with respect to symptomatology, more recent reports have a higher proportion of sleep disorder cases.

As of Oct. 10, 2000, the CADRMP received 51 domestic reports of suspected ADRs associated with ropinirole use and 17 with pramipexole. These reports were of sleep-related disturbances in 26 of the ropinirole cases and 16 of the pramipexole cases. Variants of "sudden onset of sleep" or "sleep attacks" were reported in 19 of the 26 sleep-related disturbances with ropinirole and all of the 16 cases with pramipexole. In some of the cases, patients were driving when the sudden onset of sleep occurred. No serious injuries resulted.

The sleep disorder has been described in the literature and in Canadian ADR reports in a variety of terms, namely "sleep attack," "falling asleep while driving," "narcoleptic attack" as well as "sudden onset of sleep," "irresistible sleep" and "blackout." The episodes seem to be of sudden onset and short duration, lasting only a few seconds; often, the affected patient suffers the episode with no warning symptoms such as unusual fatigue.

Both ropinirole and pramipexole continue to be available in Canada. Their conditions of use with regard to driving and operating machines were defined by Dear Health Care Professional Letters, issued in July 1999 by Boehringer Ingelheim for pramipexole and in February 2000 by SmithKline Beecham for ropinirole, in cooperation with the Therapeutic Products Programme. The letters state: "Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e.g., operating machines)."

An extensive guideline for physician evaluation of patients' ability to drive a motor vehicle safely has been published by the Canadian Medical Association and may provide useful information.[8] Unfortunately, any driving restriction placed on patients who are taking either ropinirole or pramipexole could have a significant impact on the quality of life of patients with Parkinson's disease.

Written by: Henry Moller, MD, Bureau of Licensed Product Assessment.

References

1. *Requip™, ropinirole tablets* [product monograph]. Oakville (ON): SmithKline Beecham Pharma; 1999 July 15.
2. *Mirapex®, pramipexole tablets* [product monograph]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd; 2000 Jan 31.
3. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999;52:1908-10.
4. Olanow CW, Schapira AH, Roth T. Falling asleep at the wheel: motor vehicle mishaps in people taking pramipexole and ropinirole [letter]. *Neurology* 2000;54:274.
5. Weiner WJ. Falling asleep at the wheel: motor vehicle mishaps in people taking pramipexole and ropinirole [letter]. *Neurology* 2000;54:274-5.
6. Olanow CW, Schapira AHV, Roth T. Waking up to sleep episodes in Parkinson's disease. *Movement Disord* 2000;15(2):212-5.
7. Communiqué: Ropinirole (Requip): sleep disorder. *Can Adverse Drug React Newsl* 1999;9(4):4. [Also in *CMAJ* 1999;161(7):870]
8. Canadian Medical Association. *Determining medical fitness to drive. A guide for physicians.* 6th ed. Ottawa: The Association; 2000. Available: www.cma.ca/catalog/driversguide/index.htm

Rofecoxib (Vioxx): a year in review

Rofecoxib (Vioxx), the second selective cyclo-oxygenase (COX)-2 inhibitor made available in Canada, was approved for sale in October 1999 to treat acute and chronic signs and symptoms of osteoarthritis, relieve pain in adults and treat primary dysmenorrhea.[1] ADRs received by the CADRMP that were associated with celecoxib, the other selective COX-2 inhibitor approved for sale in Canada, in April 1999, were summarized in the April 2000 issue of this Newsletter.[2] In this issue we describe suspected ADRs associated with rofecoxib.

These nonsteroidal anti-inflammatory drugs (NSAIDs) selectively inhibit the COX-2 isoenzyme at therapeutic doses, whereas traditional NSAIDs inhibit both the COX-1 and COX-2 isoforms to varying degrees. The clinical effects of NSAIDs result primarily from inhibition of the COX-2 isoenzyme (e.g., inflammation, pain), whereas inhibition of the COX-1 isoenzyme is considered to be responsible for their toxic effects (e.g., perforations, ulcers, bleeding, renal adverse effects).[3,4]

From Oct. 25, 1999, to Nov. 23, 2000, the CADRMP received 151 domestic reports describing 417 suspected adverse reactions to rofecoxib. Of the 151 reports, 91 were classified as serious[5] (56 female, 29 male, 6 sex unknown); ages ranged from 32 to 94 years, with 48% of the patients being 65 years of age or older.

Five deaths associated with the use of rofecoxib were reported with the outcome "drug may be contributory." The reported causes of death included: unknown (2); cardiac arrest, cause of death unknown (1); hemorrhagic duodenal ulcer (1); and myocardial infarction and perforated duodenal ulcer (1). The 5 patient's ages ranged from 70 to 91 years.

Of the 151 reports received, 62 (41.1%) involved suspected gastrointestinal adverse effects, with 109 adverse reactions noted (Table 1). Although the selective COX-2 inhibitors are associated with a reduction of gastrointestinal adverse effects, practitioners must remember that these drugs still have an associated risk of gastrointestinal toxicity.[1]

Risk factors for gastrointestinal adverse effects with NSAIDs include advanced age (> 65 years), concomitant use of corticosteroids or anticoagulants, history of gastrointestinal ulceration or bleeds, use of higher doses of NSAIDs, smoking, consumption of alcohol and poor general health.[1,6]

The CADRMP received 25 reports (16.6%) involving suspected cardiovascular reactions to rofecoxib. Of these, 7 cases were of heart failure (Table 2). In each of the reported cases patients had known risk factors. Six patients required hospital care; information on the seventh patient was unavailable. Symptoms appeared within 3 weeks after the start of therapy in 5 cases. All doses were within the recommended range.

Thirty-one reports (20.5%) denoting urinary and metabolic disorders associated with the use of rofecoxib were received by the CADRMP. Five involved acute renal failure. In patients with renal dysfunction, renal prostaglandins serve as physiologic modulators to maintain renal perfusion by decreasing vascular resistance and dilating vascular beds. In addition, they are involved in sodium, potassium and water homeostasis.[1,7,8] By inhibiting renal prostaglandin synthesis NSAIDS can therefore have a deleterious effect on renal function.[1,7,8]

To minimize the risk of cardiovascular and renal adverse events, the Vioxx product monograph directs practitioners to exercise caution when prescribing selective COX-2 inhibitors to patients with fluid retention, hypertension, heart failure, left ventricular dysfunction, impaired renal function, liver dysfunction, volume-depleted states (e.g., dehydration, active diuresis, hemorrhage), those taking diuretics or angiotensin-converting-enzyme (ACE) inhibitors, and elderly patients.[1,7,8] Also, patients should be instructed to watch for signs of congestive heart failure and renal dysfunction such as swelling of the lower extremities and shortness of breath.[1]

At the time of marketing, the safety profile for any drug is not complete, but with time and use of the drug by the general population, the profile continues to develop. Health professionals are requested to report any suspect serious adverse reactions associated with rofecoxib.

Written by: K. Lynn Stienburg, BSc(Pharm), Program Coordinator, Atlantic Regional ADR Centre.

References

1. *Vioxx®*, rofecoxib [product monograph]. Kirkland (QC): Merck Frosst Canada & Co.; 2000 Sept 15.
2. McMorran M, Morawiecka I. Celecoxib (Celebrex): 1 year later. *Can Adverse Drug React Newsl* 2000;10(2):1. [Also in *CMAJ* 2000;162(7):1044-6.]
3. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;104:413-21.
4. Needleman P, Isakson PC. The discovery and function of COX-2. *J Rheumatol* 1997;24(Suppl 49):6-8.
5. *Canadian Adverse Drug Reaction Monitoring Programme guidelines for the voluntary reporting of adverse drug reactions by health professionals*. Ottawa: Therapeutic Products Programme, Health Canada. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr-guideline_e.html
6. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998;105(1B):31S-38S.
7. Tannenbaum H, Peloso PMJ, Russell AS, Marlow B. An evidence-based approach to prescribing NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis: the Second Canadian Consensus Conference. *Can J Clin Pharmacol* 2000;7(Suppl A):4A-16A.
8. Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. *Am J Med* 1999;107(6A):65S-71S.

Table 1: Suspected cardiovascular, gastrointestinal and urinary/metabolic adverse reactions* to rofecoxib (Vioxx) from 151 reports† submitted to the CADRMP between Oct. 25, 1999, and Nov. 23, 2000.

Cardiovascular (25 reports [16.6%]): Cardiac failure (7), hypertension (7), myocardial infarction (3), flushing (3), stroke (2), hypotension (2), cardiac arrest (2), angina pectoris (2), palpitation (2), arrhythmia (2), vasculitis (1), circulatory failure (1), hypertensive encephalopathy (1), hypertension aggravated (1), tachycardia (1)

Gastrointestinal (62 reports [41.1%]): Nausea (16), abdominal pain (14), gastrointestinal hemorrhage (14), melena (12), diarrhea (10), vomiting (9), mouth edema (6), hematemesis (5), dysphagia (3), dyspepsia (3), anorexia (2), gastric ulcer (2), gastritis (2), perforated duodenal ulcer (2), gastrointestinal disorder not specified (1), dry mouth (1), duodenal ulcer (1), enlarged abdomen (1), anastomotic ulcer (1), intestinal ulceration (1), flatulence (1), mucositis (1), esophagitis (1)

Urinary/metabolic (31 reports [20.5%]): Peripheral edema (13), NPN increased (7), acute renal failure (5), edema (3), hyperglycemia (3), hyponatremia (3), edema dependent (2), BUN increased (2), generalized edema (2), urinary tract infection (1), nephrosis (1), anuria (1), weight decrease (1), weight increase (1), hyperkalemia (1), creatine phosphokinase increased (1), dehydration(1), hypoglycemia (1)

Note: **NPN** = serum creatinine, **BUN** = blood urea nitrogen.

* Based on the "preferred term" in the World Health Organization (WHO) Adverse Drug Reaction Dictionary (WHOART)

† Several reaction terms may be listed per ADR report.

Table 2: Summary of 7 case reports involving suspected heart failure associated with rofecoxib (Vioxx) submitted to the CADRMP between Oct. 25, 1999, and Nov. 23, 2000

Case	Age/ sex	Reported reactions*	Outcome†	Medical history	Concomitant medications
1	85/M	Congestive heart failure	Unknown	Pulmonary embolism, coronary artery disease, hypertension	Cardizem CD, Isordil, nitroglycerin
2	78/M	Fluid retention in tissues, heart failure, hyponatremia, peripheral edema	Recovered without sequelae	Diabetes mellitus, benign prostatic hyperplasia, rheumatoid arthritis	Methotrexate, Pepcid, prednisolone, Tylenol
3	65/F	Shortness of breath, congestive heart failure, vomiting	Unknown	MI, CABG, arthritis, hypothyroidism	Demerol, Lasix, levothyroxin, Lithium, Losec, perindopril, sertraline
4	84/M	Congestive heart failure	Recovered without sequelae	Atrial fibrillation, COPD	Betoptic S
5	66/F	Heart failure	Recovered without sequelae	Hypertension, obesity	Lasix, Sectral
6	42/M	Congestive heart failure aggravated	Not yet recovered	Cardiac output low, cardiomyopathy, congestive heart failure, mitral valve prolapse	Coumadin, carvedilol, furosemide, potassium chloride.
7	77/M	Anuria, congestive heart failure, blood creatinine level increased, acute renal failure	Not yet recovered	Cardiomyopathy, congestive heart failure, hypertension, NIDDM, polyclonal gammopathy, renal insufficiency	Lopresor, Novasen, enalapril, furosemide, glyburide, metformin

Note: MI = myocardial infarction, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, NIDDM = non-insulin-dependent diabetes mellitus.

* Based on the "preferred term" in the World Health Organization (WHO) Adverse Drug Reaction Dictionary (WHOART)

† At the time of reporting.

COMMUNIQUÉ

The CADRMP wishes to provide feedback and increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the official Canadian product monograph.

Warfarin and glucosamine: interaction
An increase in the International Normalized Ratio (INR) was noted when glucosamine was administered to patients receiving warfarin. INR values decreased when glucosamine was stopped.

DRUGS OF CURRENT INTEREST

The purpose of the Drugs of Current Interest (DOCI) list is to stimulate reporting for a selected group of marketed drugs in order to identify drug safety signals. The maintenance of this list by the CADRMP facilitates regular monitoring and constitutes one element of post-approval assessment activities.

abacavir (Ziagen)
alteplase (Activase rt-PA)
celecoxib (Celebrex)
clopidogrel (Plavix)
delavirdine (Rescriptor)
efavirenz (Sustiva)
Hypericum perforatum (St. John's Wort)
indinavir (Crixivan)
melanoma theraccine (Melacine)
naratriptan (Amerge)
nevirapine (Viramune)
oseltamivir (Tamiflu)
pioglitazone (ACTOS)
ritonavir (Norvir)
rituximab (Rituxan)
rofecoxib (Vioxx)
rosiglitazone (Avandia)
saquinavir (Invirase)
trastuzumab (Herceptin)
zaleplon (Starnoc)
zanamivir (Relenza)
zolmitriptan (Zomig)

If you have observed any suspected ADRs with the drugs in the Communiqué or DOCI list, *please report them* to the :

Canadian Adverse Reaction Monitoring Program (CADRMP)
Adverse Reaction Review and Information Unit
Bureau of Licensed Product Assessment
AL: 0201C2, Ottawa, ON K1A 1B9
Tel: (613) 957-0337 Fax: 613 957-0335
cadrmp@hc-sc.gc.ca
or to a participating regional ADR centre.

The ADR form is available from the *Compendium of Pharmaceuticals and Specialties* and the National and Regional ADR Centres, and at:

http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf
http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr_guideline_e.pdf

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Canada

Please Note: A voluntary reporting system thrives on intuition, lateral thinking and open mindedness. Most adverse drug reactions (ADRs) can only be considered to be suspicions, for which a proven causal association has not been established. Because ADRs are underreported and because a definite causal association cannot be determined, spontaneous ADR reports cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless valuable as a source of potential new and undocumented signals. Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles. Furthermore, the Therapeutic Products Programme monitors and assesses suspected ADRs as a means of continuously evaluating drug safety profiles. Regulatory decisions are not made within the context of this newsletter.

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